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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,769	VARNUM ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-49,52,53 and 55-61* is/are pending in the application.

4a) Of the above claim(s) *3,4,6-9,12-31,39,41,43,45,60 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,32-38,40,42,44,46-49,52 and 55-59* is/are rejected.

7)☒ Claim(s) *10 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

2. Applicant's amendment to the claims, filed December 8, 2006, has been entered.

   Claims 11, 50, 51 and 54 have been canceled.

   Claims 5 and 56-59 have been amended.

   Claims 1-10, 12-49, 52, 53 and 55-61 are pending.

   Claims 1, 2, 5, 10, 32-38, 40, 42, 44, 46-49, 52, 53 and 55-59 are under consideration in the instant application as they read on the elected invention of Group III, an antibody that binds IL-1R1 comprising SEQ ID NOs: 16, 18, 63, 66, 69, 71, 73 and 75.

   Claims 3, 4, 6-9, 12-31, 39, 41, 43, 45, 60 and 61 have been withdrawn as being drawn to a non-elected invention.

3. This Office Action is in response to Applicant's amendment to the claims and remarks filed December 8, 2006.

   The rejections of record can be found in the previous Office Action, mailed June 9, 2006.

   The text of those sections of Title 35 U.S.C. not included in this Action can be found in a prior Office action.

   The prior rejection of claim 11 under 35 U.S.C. § 112, 1st paragraph, new matter has been withdrawn in view of applicants amendment to the claims.

   New Grounds of Rejection are set forth below.

4. ***Claims 1, 2, 5, 32-38, 40, 42, 44, 46-49 and 52 stand rejected under 35 U.S.C. 112, first paragraph,*** as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to ***make and/or use*** the invention, ***essentially for the reasons of record.***

   The instant claims recite, or depend from claims which recite, antibodies comprising less than the complete light and heavy chain variable domains.

Applicant repeats their argument essentially as put forth in their remarks of April 14, 2006.

Applicant's arguments have been considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action.

One argument that appears to be new in applicant's current remarks is that the Janeway reference provided with the first action on the merits of October 11, 2005 allegedly does not sufficiently support the position that the instantly claimed antibodies comprising less than a pair of defined, complete heavy and light chain variable domains would bind IL-1R1.

With respect to the Janeway reference, please see the pages from Janeway attached herewith in particular pages 100-102 (Janeway et al., Immunobiology, 5th Ed., Garland Science, pp. 94-105 (2001)) which sufficiently support the position that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Another argument that appears to be newly put forth in applicant's current remarks is that several U.S. Patents have issued which claim antibodies by identifying a single CDR domain and therefore, "the Patent Office has recognized that antibodies can be claimed by identifying a single CDR domain."

This argument is not found convincing because each patent application is considered on its own merits, and applicant's argument for this particular case have not been found convincing, essentially for the reasons of record. Moreover, it is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

Moreover, applicant asserts that the instant specification provides an "extensive discussion" on page 33, line 16 to page 41, line 10 (presumably "extensive discussion" refers to a discussion of the instantly claimed antibodies or methods for making the claimed antibodies).

Pages 33-41 of the instant specification have been reviewed by the examiner; however, most of the disclosure on these pages is related to methods of making antibodies comprising complete variable heavy and light chains, e.g., monoclonal antibodies, chimeric antibodies, human antibodies etc. These pages do not provide *objective evidence* to indicate that any of the *particular* antibody variable regions disclosed in the instant claims or specification can bind to antigen on its own, in the absence of a complementary heavy or light chain variable region containing all three CDRs. Moreover, these pages do not provide sufficient guidance or direction to enable one of skill in the art, *without undue experimentation*, to make an antibody that specifically binds IL-1R1 starting with molecules comprising *a subset* of the six CDRs required for antibody binding to antigen with a reasonable expectation of success.

Thus, in view of the lack of predictability of the art to which the invention pertains, the lack of working examples, and the level of skill and knowledge in the art, undue experimentation would be required for one of skill in the art to make the claimed antibodies.

5. ***Claims 5, 32-38 and 40 are rejected under 35 U.S.C. 112, first paragraph,*** as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, ***to make and/or use*** the invention. ***This is a New Grounds of Rejection.***

Claim 5, and dependent claims thereof, recite "an isolated human antibody that binds IL-1R1 wherein the antibody comprises...a heavy chain variable region comprising an amino acid sequence that has ***at least 90%*** sequence identity to the amino acid set forth in ***SEQ ID NO: 16***...and a light chain...***at least 90%***...identity to ***SEQ ID NO: 18***," wherein the antibody specifically binds IL-1R1 and, ***"wherein the antibody inhibits binding of IL-1β to IL-1R1."***

Claim 5, given its broadest reasonable interpretation consistent with the instant specification, reads on antibodies with ***up to 12-13 amino acids changes*** in each of SEQ ID Nos: 16 and 18 (see instant specification, page 21, 2nd paragraph and pages 27-33), wherein the resultant antibody "inhibits binding of IL-1β to IL-1R1".

The instant specification discloses at pages 17, 1st paragraph, that antibodies of the invention may contain deletions, additions, or substitutions of one or more amino acids.

The instant specification further discloses two antibodies, "26F5", which comprises SEQ ID Nos: 10 and 12, and "27F2", which comprises SEQ ID NOs: 14 and 12, that share many properties with the antibody comprising SEQ ID NOs: 16 and 18 of the instant claims, the "15C4" antibody (see instant specification pages 72-78).

However, while the 26F5 and 27F2 antibodies are functionally similar to the antibody comprising SEQ ID NOs: 16 and 18 of the instant claims, these antibodies were ***not*** derived from the antibody comprising SEQ ID NOs: 16 and 18, rather all three of these antibodies were isolated by immunizing mice transgenic for human immunoglobulin genes with IL-1R1 purified from, e.g., insect or mammalian cells, and screening hybridomas generated from these mice for anti-IL-1R1 antibodies (see instant specification pages 68-71).

Indeed, the heavy and light chains of the 26F5 and 27F2 antibodies have, ***at best, 53% identity and 65% identity*** with heavy and light chains of the instantly claimed antibody, SEQ ID NOs: 16 and 18, respectively (see attached alignment). The substantial differences between these antibodies is a consequence of these antibodies being derived from ***completely different germline genes***, **i.e.,** the heavy and light chains of the instantly claimed antibody were derived from the ***V_h5-51 and V_lA10 germline genes*** while the heavy and light chains of the 26F5 and 27F2 antibodies were derived from the ***V_h3-30.1 and V_lL6 germline genes***.

Thus, the antibody comprising SEQ ID NOs: 16 and 18 differs from the 26F5 and 27F2 antibodies in the sequences of the CDRs ***AND*** in the sequences of the framework regions.

As such, the overall structural differences between these antibodies is so great that the skilled artisan would not be able to infer from these aligned sequences which amino acids are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and therefore, the ordinary artisan would not know how to make deletions, insertions or substitutions of SEQ ID NOs: 16 and 18 which do not ablate the ability of the resultant antibody to specifically bind IL-1R1 and inhibit IL-1β binding to IL-1R1.

Thus, the instant specification does not provide sufficient guidance or direction as to the general tolerance to modification and extent of such tolerance in the variable regions; the specific positions of the variable regions which can be predictably modified and which regions are critical for maintaining IL-1R1 binding/IL-1β inhibitory function. Moreover, the instant specification provides insufficient evidence or nexus that would lead the skilled artisan to predict which amino acid changes would result in the creation of an antibody derivative comprising amino acid sequences at least 90% identical to SEQ ID NO:16 and 18 that binds IL-1R1 and inhibits IL-1β binding to IL-1R1.

Without guidance or direction as to which sequences in the variable region can be altered, it would require undue trials and errors to make the antibodies encompassed by the instant claims.

An example of the unpredictability of making changes to the sequence of an antibody is provided by Rudikoff et al who teach that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79: 1979-1 983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Furthermore, Colman P. M. (Research in Immunology, 145:33-36, 1994) teach that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column).

Likewise, at least in some cases, even minor amino acid changes to the framework region of an antibody can compromise its biological activity or structural specificity as shown by Chien et al., (Proc Natl Acad Sci U S A. 1989 Jul;86(14):5532-6), which describes how changing a single amino acid residue outside and distant from the antibody antigen binding site is nonetheless capable of completely eliminating antigen binding (see Chien, page 5536, 3rd paragraph). Chien concludes, "Our results and observations by others...suggest that residues distant from the binding site may play an important role in the specificity and affinity of the antigen-binding site." (see Chien, page 5536, 3rd paragraph).

In view of the lack of predictability of the art to which the invention pertains, the lack of working examples, and the level of skill and knowledge in the art, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed antibodies in a manner reasonably correlated with the scope of the claims. Without such guidance, the changes which can be made in the protein's structure and still maintain antigen-binding function is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen. Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F, 2d 1200, 18 USPQ 101 6 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

In summary, undue experimentation would be required to practice the instantly claimed invention.

6. ***Claims 1, 2, 32-38, 40, 42, 44, 46-49 and 52 stand rejected under 35 U.S.C. 112, 1st paragraph,*** as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had ***possession*** of the claimed invention, ***essentially for the reasons of record.***

The instant claims recite, or depend from claims which recite, antibodies comprising less than the complete light and heavy chain variable domains.

Applicant repeats their argument essentially as put forth in their remarks of April 14, 2006. In particular, applicant indicates that, "as discussed in the Response to the previous Office Action, those of skill in the art recognize that antibodies do not always require a light chain, a heavy chain, and all six CDRs from the light and heavy chains for binding specificity of an antibody to a particular epitope."

Applicant's arguments have been considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action.

As indicated in the previous Office Action, Applicant's argument is not found persuasive because the instant specification does not indicate that any of the heavy or light chain variable regions of the *particular* anti-IL-1R1 antibody species disclosed can bind to antigen on its own, in the absence of its complementary heavy or light chain variable region. The instant specification does not demonstrate possession of the instantly claimed invention.

Moreover, applicant asserts that because a number of antibodies comprising full heavy and light chain variable domains with all three CDRs that bind IL-1R1 are structurally described and functionally characterized in the instant specification and, "since the art of making antibodies is considered to be more mature, i.e., more predictable, than some other areas of biotechnology, and Applicants teach many particular sequences of IL-1R1 binding antibodies, one of skill in the art would conclude that Applicants were in possession of the common attributes of the claimed antibodies."

However, it does not appear based upon the disclosure of several anti-IL1R1 antibodies comprising full heavy and light chain variable domains with all three CDRs that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the claimed genus, i.e., the particular ***structural or other physical and/or chemical characteristics that are critical to the function*** of the claimed antibodies, in view of the extensive variation permitted within the claimed genus of anti-IL1R1 antibodies comprising less than the complete light and heavy chain variable domains.

The structure of the antibodies disclosed in the instant specification is consistent with the principals of antibody structure and function as described by Janeway et al., Immunobiology, 5th Ed., Garland Science, pp. 94-105 (2001), see in particular, page 100-102. While antibodies can be isolated that do not require both variable domains to bind antigen, the antibodies disclosed in the instant specification do not appear to have this ability.

It is noted that conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Accordingly, applicant has not demonstrated possession of the instant claims.

7. ***Claims 5, 32-38, 40 are rejected under 35 U.S.C. 112, 1st paragraph,*** as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had ***possession*** of the claimed invention, essentially for the reasons of record. **This is a New Grounds of Rejection.**

Claim 5, and dependent claims thereof, recite "an isolated human antibody that binds IL-1R1 wherein the antibody comprises...a heavy chain variable region comprising an amino acid sequence that has ***at least 90%*** sequence identity to the amino acid set forth in ***SEQ ID NO: 16***...and a light chain...***at least 90%***...identity to ***SEQ ID NO: 18***," wherein the antibody specifically binds IL-1R1 and, ***"wherein the antibody inhibits binding of IL-1β to IL-1R1."***

Claim 5, given its broadest reasonable interpretation consistent with the instant specification, reads on antibodies with ***up to 12-13 amino acids changes*** in each of SEQ ID Nos: 16 and 18 (see instant specification, page 21, 2nd paragraph and pages 27-33), wherein the resultant antibody "inhibits binding of IL-1β to IL-1R1". For the purposes of examination under 35 U.S.C. § 112, 1st paragraph, written description, it is noted that the phrase, "inhibits binding of IL-1β binding to IL-1R1," given its broadest reasonable interpretation consistent with the instant specification, includes ***any*** degree of inhibition, e.g. from ≤1% to 100%, of ***IL-1β binding to IL-1R1*** (see instant specification page 26, 1st paragraph where "substantially inhibits" is defined; however it is noted that "inhibits" not "substantially inhibits" is claimed).

Thus, the instant claim encompass in their breadth antibodies ***with up to 12-13 amino acid changes*** in each of SEQ ID Nos: 16 and 18 that retain ***any*** ability to inhibit IL-1β binding to IL-1R1. Thus, the genus of claimed antibodies is extensive.

The instant specification discloses at pages 17, 1st paragraph, that antibodies of the invention may contain deletions, additions, or substitutions of one or more amino acids.

The instant specification further discloses two antibodies, "26F5", which comprises SEQ ID Nos: 10 and 12, and "27F2", which comprises SEQ ID NOs: 14 and 12, that share many properties with the antibody comprising SEQ ID NOs: 16 and 18 of the instant claims, the "15C4" antibody (see instant specification pages 72-78).

However, while the 26F5 and 27F2 antibodies are functionally similar to the antibody comprising SEQ ID NOs: 16 and 18 of the instant claims, these antibodies were ***not*** derived from the antibody comprising SEQ ID NOs: 16 and 18, rather all three of these antibodies were isolated by immunizing mice transgenic for human immunoglobulin genes with IL-1R1 purified from, e.g., insect or mammalian cells, and screening hybridomas generated from these mice for anti-IL-1R1 antibodies (see instant specification pages 68-71).

Indeed, the heavy and light chains of the 26F5 and 27F2 antibodies have, ***at best, 53% identity and 65% identity*** with heavy and light chains of the instantly claimed antibody, SEQ ID NOs: 16 and 18, respectively (see attached alignment). The substantial differences between these antibodies is a consequence of these antibodies being derived from ***completely different germline genes***, **i.e.,** the heavy and light chains of the instantly claimed antibody were derived from the ***V_h5-51 and V_lA10 germline genes*** while the heavy and light chains of the 26F5 and 27F2 antibodies were derived from the ***V_h3-30.1 and V_lL6 germline genes***.

Thus, the antibody comprising SEQ ID NOs: 16 and 18 differs from the 26F5 and 27F2 antibodies in the sequences of the CDRs ***AND*** in the sequences of the framework regions. As such, the overall structural differences between these antibodies is so great that the skilled artisan would not be able to infer from these aligned sequences which amino acids are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification).

It does not appear based upon the disclosure of only the anti-IL1R1 antibody comprising SEQ ID NOs: 16 and 18 of the instant claims that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the extensive variation permitted within the claimed genus of antibodies.

Moreover, the instant specification does not provide adequate written description of the broad genus of antibodies encompassed by claim 5, and dependent claims thereof, because relevant identifying characteristics for the antibody mutants encompassed by this claim, such as the particular ***structural or other physical and/or chemical characteristics that are critical to the function*** of the claimed antibody, i.e., binding IL-1R1 and inhibiting IL-1β binding, are not disclosed.

Since the amino acid sequence of a protein determines its structural and functional properties the changes that can be tolerated in a antibody while retaining similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function.

The instant specification does not provide sufficient direction or guidance as to which particular amino acid residues of the claimed antibody can be changed and the specific nature of the change, i.e., deletion, insertion or substitution, without ablating the ability of the antibody to specifically bind IL-1R1 and inhibit IL-1β binding to IL-1R1. Without this guidance or direction the skilled artisan would not consider applicant to be in possession of the claimed genus of antibodies because the skilled artisan recognizes that even seemingly minor changes made without guidance or direction as to the relationship between the particular amino acid sequence of the instantly claimed antibody and its ability to bind antigen, can dramatically affect antigen-antibody binding.

For example, Rudikoff et al. (Proc. Natl. Acad. Sci. USA, 79: 1979-1 983, March 1982) provides an example of how even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Similarly, Coleman P. M. (Research in Immunology, 145:33-36, 1994) teach that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column).

Likewise, in at least some cases, minor amino acid changes to the framework region of an antibody can compromise its biological activity or structural specificity as shown by Chien et al., (Proc Natl Acad Sci U S A. 1989 Jul;86(14):5532-6), which describes how changing a single amino acid residue outside and distant from the antibody antigen binding site is nonetheless capable of completely eliminating antigen binding (see Chien, page 5536, 3rd paragraph). Chien concludes, "Our results and observations by others...suggest that residues distant from the binding site may play an important role in the specificity and affinity of the antigen-binding site." (see Chien, page 5536, 3rd paragraph).

Thus, neither the instant specification nor the knowledge in the art are sufficient to extrapolate from a given anti-IL1R1 antibody, such as the antibody comprising SEQ ID NO: 16 and 18, to ***all*** other antibodies ***with up to 12-13 amino acid changes*** in SEQ ID Nos: 16 and 18 that retain ***any*** of the ability of the parent antibody (SEQ ID NOs: 16 and 18) to bind IL-1R1, and thus one skilled in the art could not reasonably conclude that applicant had ***possession*** of the claimed invention.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, MPEP 2163 II.A.3a.ii.

See also, Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997), "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. **Claims 55 and 56 stand rejected under 35 U.S.C. § 102(e)** as anticipated by Dower et al. (U.S. Patent No. 6,511,665) as evidenced by Vigers et al. (Nature. 1997 Mar 13;386(6621):190-4), essentially for the reasons of record.

As a preliminary matter, it is noted that while claim 55 lacks transitional language it does refer to "an antibody that specifically binds ***the*** polypeptide of SEQ ID NO: 76" and therefore is being read as encompassing an antibody that specifically binds ***a*** polypeptide wherein ***the*** polypeptide is SEQ ID NO: 76.

Moreover, claim 56, as amended, recites "the antibody of claim 55, wherein the antibody specifically binds to ***a region of IL-1R1*** that comprises the amino acid sequence YSV". Since, "a region of IL-1R1" cannot be broader than "***the*** polypeptide of SEQ ID NO: 76", an antibody that "specifically binds to a region of IL-1R1," given its broadest reasonable interpretation consistent with the instant specification, is being interpreted as an antibody that specifically binds some segment of amino acids encompassed by SEQ ID NO: 76 (SEQ ID NO: 76 inclusive), wherein the segment of polypeptide bound by the antibody includes the YSV sequence, however, the antibody may or may not actually bind to the "YSV" sequence.

Applicant's arguments have been considered in their totality but have not been found convincing, essentially for the reasons of record.

Applicant argues that while Dower teaches, "antibodies ***against the soluble truncated form of IL-1 receptor are preferred***...[Dower] does not mention ***the specific sequence described in SEQ ID NO: 76*** as having any particular importance for making antibodies against soluble IL-1 receptor."

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

While it is true that Dower does not single out the particular SEQ ID NO: 76 polypeptide sequence as being of particular importance for making anti-IL1R1 antibodies, Dower does disclose that antibodies against soluble truncated forms of IL-1R1 are preferred, and Dower teaches said antibodies may be utilized therapeutically to block the binding of IL-1 to its receptor (see entire document, in particular, column 11, lines 16-17 and column 5, lines 27-36 and column 15, lines 7-10). Dower also teaches that said antibodies may be human antibodies (see in particular, column 10, last paragraph through column 14 and claim 12).

Dower further teaches a method for determining if an anti-IL1R1 antibody is capable of inhibiting the binding of an IL-1 ligand to IL-1R1 expressed on the surface of cell (see, in particular, column 30 part G to column 31).

As evidenced by Vigers et al, one portion of IL-1α and IL-1β, "site B", which is one of two parts of IL-1α/β essential for interaction with IL-1R1, makes extensive contacts exclusively with "domain three" of soluble IL-1R1, which encompasses SEQ ID NO:76 (see Vigers, entire document, particularly Results on page 191-193).

Given that Dower teaches human antibodies against soluble truncated IL-1R1, and that antibodies against this portion of IL-1R1 may be utilized therapeutically to block the binding of IL-1 to its receptor, and given that the teachings of Vigers that IL-1α/β bind IL-1R1 at essentially two receptor surfaces which interact with either "site A" or "site B" of IL-1α/β ligands, the ordinary artisan making the antibodies of Dower would necessarily arrive at anti-IL-1R1 antibodies that bind the surface of IL-1R1 involved in IL-1α/β "site A" binding and the surface of IL-1R1 involved in IL-1α/β "site B" binding. Therefore the skilled artisan, employing the teachings of Dower would necessarily arrive to the claimed invention.

Applicant further argues that Dower fails to "***actually disclose or make*** any of these ***preferred antibodies***." Thus, applicant concludes "[s]ince ***no antibodies made in [Dower] were tested for the ability to block binding of IL-1 to its receptor***, it is simply speculation that any such antibody would bind this portion of the receptor as presently claimed." (emphasis added).

In response, it is noted that Dower does not have to ***actually make the claimed antibodies*** in order to anticipate the claimed invention. Rather, Dower may simply teach ***how to make*** the claimed antibodies and still anticipate the claimed invention. As stated in MPEP § 2121.01, "[a] reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

Nevertheless, in contrast to applicant's assertions, it is noted that Dower did actually make the *preferred antibodies* that (1) recognize soluble human IL-1R1 and (2) inhibit the binding of IL-1α to IL-1R1 (see Table 1, hIL1Rm1 and hIL1Rm10 and column 30 parts E and G to column 31). However, it is further noted that the antibodies made by Dower were murine monoclonal antibodies rather than human monoclonal antibodies.

Since the Office does not have a laboratory to test the human anti-IL-1R1 antibodies of Dower, it is applicant's burden to show that the reference antibodies do not specifically bind to the polypeptide of SEQ ID NO: 76. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. **Claims 55 and 56 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Dower et al. (U.S. Patent No. 6,511,665) in view of Vigers et al. (Nature. 1997 Mar 13; 386 (6621): 190-4) and Schreuder et al. (Nature. 1997 Mar 13;386(6621):194-200).
This is a New Grounds of Rejection.

As a preliminary matter, it is noted that while claim 55 lacks transitional language it does refer to "an antibody that specifically binds ***the*** polypeptide of SEQ ID NO: 76" and therefore is being read as encompassing an antibody that specifically binds ***a*** polypeptide wherein ***the*** polypeptide is SEQ ID NO: 76.

Moreover, claim 56, as amended, recites "the antibody of claim 55, wherein the antibody specifically binds to ***a region of IL-1R1*** that comprises the amino acid sequence YSV". Since, "a region of IL-1R1" cannot be broader than "***the*** polypeptide of SEQ ID NO: 76", an antibody that "specifically binds to a region of IL-1R1," given its broadest reasonable interpretation consistent with the instant specification, is being interpreted as an antibody that specifically binds some segment of amino acids encompassed by SEQ ID NO: 76 (SEQ ID NO: 76 inclusive), wherein the segment of polypeptide bound by the antibody includes the YSV sequence, however, the antibody may or may not actually bind to the "YSV" sequence.

Dower teaches that antibodies against soluble truncated forms of IL-1R1 are preferred, and that said antibodies may be utilized therapeutically to block the binding of IL-1α and IL-1β to their common receptor, which is useful, for example, to regulate IL-1α and IL-1β mediated inflammation (see entire document, in particular, column 1, 3rd paragraph, column 11, lines 16-17 and column 5, lines 27-36 and column 15, lines 7-10). Dower further teaches human anti-IL-1R1 antibodies (see in particular, column 10, last paragraph through column 14 and claim 12). Dower further teaches a method for determining if an anti-IL1R1 antibody is capable of inhibiting the binding of an IL-1 ligand to IL-1R1 expressed on the surface of cell (see, in particular, column 30 part G to column 31).

The instant claims differ from Dower in that they explicitly recite that the claimed antibodies bind SEQ ID NO: 76.

Vigers teaches that both IL-1α and IL-1β contain a constellation of amino acids referred to as "site B", which is one of two parts of IL-1α/β essential for interaction with IL-1R1. Vigers further teaches that "site B" of IL-1α/β makes extensive contacts exclusively with "domain three" of soluble IL-1R1 (see entire document, in particular page 191 right column, 2nd paragraph to page 192, 1st paragraph).

Schreuder teaches that IL-1α/β binds poorly to a truncated IL-1R1 expressed on the surface of a cell wherein the truncated IL-1R1 lacks "domain three". Thus, Schreuder concludes IL-1α/β need "domain three" of IL-1R1 for high affinity binding, which "suggests that domain 3 strongly interacts with IL-1 agonists." (see entire document, in particular page 199, left column, 4th paragraph and Methods on page 199).

Vigers and Schreuder both teach that "domain three" of IL-1R1 begins around amino acid 207-210 of IL-1R1, and extends to at least amino acid 308-311 (see, in particular, Vigers Figure 1 and Schreuder Figure 2).

Given the reference teaching concerning the therapeutic utility of blocking the binding of IL-1α and IL-1β to IL-1R1 by making antibodies to the extracellular domain of IL-1R1, and the essential role "domain three" of IL-1R1 in IL-1α/β binding, it would have been obvious to the ordinary artisan to prepare a human antibody that binds the extracellular domain of IL-1R1.

More particularly, the ordinary artisan would have been motivated to prepare an antibody that binds "domain three" of IL-1R1 given that Vigers demonstrates via X-ray crystallography that "site B" of IL-1α/β, which was well known in the prior art to be required for the interaction of IL-1α/β with IL-1R1 (see Vigers, page 191, left column, 2nd paragraph, to page 192, right column), interacts ***exclusively*** with "domain three" of IL-1R1.

One of ordinary skill in the art would have been further motivated to produce anti-IL-1R1 antibodies against "domain 3" of IL-1R1 in particular because Schreuder demonstrates that "domain three" of IL-1R1 is essential for high affinity IL-1α/β binding to IL-1R1 in solution.

Since "domain three" of IL-1R1 begins around amino acid 207-210 of IL-1R1, and extends to at least amino acid 308-311, human antibodies that bind "domain three" of IL-1R1 as taught by Dower in view of Vigers and Schreuder would also bind SEQ ID NO: 76, which corresponds to amino acids 226-336 of IL-1R1.

Furthermore, given the teachings of Dower regarding making human antibodies against soluble truncated IL-1R1 to block IL-1α/β receptor binding, the ordinary artisan, in making the antibodies of Dower would naturally create anti-IL-1R1 antibodies that bind the surface of IL-1R1 involved in IL-1α/β "site A" binding and the surface of IL-1R1 involved in IL-1α/β "site B" binding. Accordingly, the skilled artisan, employing the teachings of Dower would naturally create the claimed invention, even without specifically targeting domain 3 as taught by Vigers and Schreuder.

Thus, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Accordingly, the instant claims are unpatentable over Dower in view of Vigers and Schreuder.

11. No claim is allowed.

However, claim 10 is objected to because it depends on rejected claim 5, and would be allowable if rewritten in independent form.

Furthermore, claim 53 is objected to because it depends on rejected claim 46 and because it recites SEQ ID NOs not included in elected Group III. Claim 53 would be allowable if rewritten in independent form such that it only recites the elected SEQ ID Nos and includes all of the limitations of the base claim and any intervening claims.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m..
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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March 5, 2007

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